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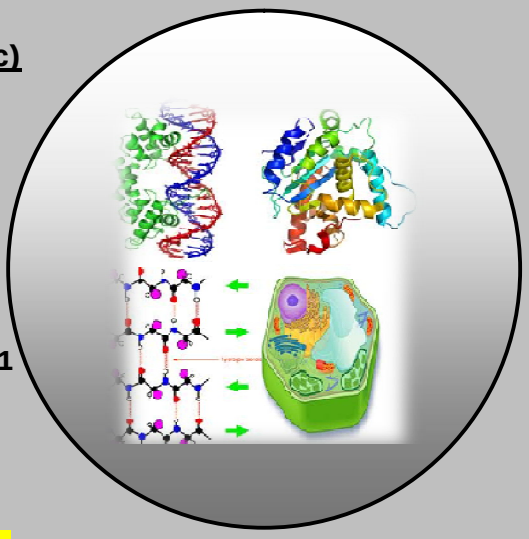

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Self-Association of Caffeine (CA) and its Hetero-Association with Polyphenols and Drugs

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ABSTRACT

This review deals with the self-association of caffeine and its hetero-association with polyphenol molecules and aromatic drugs. The various spectroscopic techniques and models developed for analysis the self-association and hetero-association constants, thermodynamic properties and structural features of the complexes were reviewed. The review provides useful information for pharmaceutical and food companies in order to design advanced and controllable drugs and foods.
Key Words: - Caffeine, polyphenols, Aromatic Drugs, Hetero-Association, Spectroscopy and Models.

INTRODUCTION

Caffeine (1, 3, 7-trimetylxanthine) is bioactive compound naturally available in leaves, seeds and fruits of 63 plant species (Hiroshi and Alan, 2006; Anthony et al., 1997; Belay, 2011; Manch et al., 2004). The most common sources are coffee beans, cocoa beans, cola nuts; tea leaves (Spiller, 1984; Anthony et al., 1997; Hiroshi and Alan, 2001). The statistical study in the United States has reported that average caffeine intake among adult consumers varies from 106 to 170 mg/day which is the major concern in the long run (Knight et al., 2004). Caffeine acts as a psychotropic drug which is also consumed by significant population of children and women during pregnancy and childbirth (Gianluigi and Steven, 2000). Long term intake of caffeine is known to affect memory and performance of human brain, especially in due course of withdrawal which then leads to decrease attentiveness, increase cloudiness of the brain (Peter and Claire, 1998; Gianluigi and Steven, 2000; Hiroshi and Alan, 2001).

It has also adverse effects such as increase frequencies of headaches and fatigue during caffeine withdrawal (Roland and Phillip, 1988; Paul et al., 2000).

In addition to the psychological effects of caffeine on human beings, the relatively high consumption of caffeine, and its abundance in dietary substances, has stimulated many researchers due to biological activity of CA results from the interaction with polyphenols, drugs and biopolymers, such as enzymes and nucleic acid and the other in cell systems. For example, it was found that CA inhibits DNA synthesis increases chromatin condensation and causes other cellular effects. On the other hand, when caffeine is administered together with aromatic cytotoxic drugs (such as doxorubicin, ethidium bromide, novantrone) there are a remarkable reduction in vitro toxicity of the drugs acting on nuclear DNA (Piosik et al, 2002; Evstgneev et al., 2006; Traganos et al., 1991). Furthermore, the direct complexation between caffeine and some aromatic drugs may also modify the pharmacokinetic properties of the drugs or lead to chemical degradation. This review, therefore deals with the various reports on the self-association of caffeine and its complexation with polyphenol molecules and aromatic drugs

Self-Association of Caffeine (CA)

Caffeine exists in a monomer form in water solution only at dilute solution. The molecules have the ability to interact with each other in aqueous media at the concentrations above 0.01 M and these associations were reported using various techniques such as UV-Vis spectrophotometer, FT-IR, and NMR (D'Amelio et al., 2009; Davies et al., 1996; Davies et al., 1999; Davies et al., 2001; Horman et al., 1984; Horman et al., 1985; Poltev et al., 2004; Bolotin et al., 2006; Frizsche et al., 1980; Falke et al., 1990). The thermodynamic properties and structure for the concentration dependent self-association of caffeine were determined by (Davies et al., 1996; Davies et al., 1999; Davies et al., 2001) using NMR spectroscopy. The mean value for the self-association constant determined by this technique is 11.8 L mol^{-1}. Furthermore, the self-association of this compound is also determined by NMR (four proton chemical shift) of caffeine molecules by (Horman Dreux, 1984; Davies et al., 1996).

The association constants of caffeine also determined by UV-Vis spectrophotometric using modified Benesani-Hildebrand model (Baranovski and Bolotin, 2007; Barnoovsky et al., 2009). The determined association constants by this technique are 12.2 and 17 M^{-1} in the hetero-association of caffeine with Eithidium Bromide and Riboflavin drugs respectively. The other technique to study the self-association of caffeine was the FT- IR developed by (Falke et al., 1998). In this study the association constant was 158.1 M^{-1}. The self-association constant reported by this technique is higher as compared with other techniques.

The most caffeine dimer structure proposed by various techniques are similar and the common proposed are the molecules of CA are aggregate in aqueous solution by plane-to-plane stacking (Danilov and Shestopalova, 1989; Falke et al., 1998; Davies et al., 2001) and these kind of stacking interactions are usually an important in connection with the pharmacological action of caffeine and for the interaction between CA and nucleic acids.

Hetero-Association of Caffeine (CA) with Polyphenol Molecules

The molecules of CA also interact with polyphenols molecules and aromatic hydroxy acids such as methyl gallate, 3-nitrobenzic acid (Martin et al., 1986), 5-chlorosaliccylic acid (Shefter, 1968), pyrogallol (Amone and Marchessault, 1968), tea chatechins (EGCg, ECg, EGC and EC) (Hayashi et al., 2004), theaflavin (Charlton et al., 2000), gallic acid and quercitin (Jostl et al., 2005). From previous research reports many polyphenols from black tea and coffee form complexes with caffeine as reported by (Horman et al., 1972; Martin et al., 1986; Martin et al., 1987). The binding constants and binding energy of the major tea polyphenols with caffeine complex have been also reported by (Hayashi et al., 2004) using ^{1}H-NMR spectroscopy. The results of this study revealed that the stoichimetric ratio of the complexation between tea catechins (EGCg, ECg, EGC and EC) and caffeine was 1:1. The free energy ($-\Delta G$) values for binding in water at 301 K were 2.7, 2.6, 2.2 and 2 kcal/mol. By similar method other researchers were also reported the complexation of CA and other purine alkaloids with chlorogenate compounds (Kappeler et al., 1987).

The equilibrium constant for the complexation of CA with major polyphenolic constitutes of green coffee beans were determined early in water solution by spectrophotometric method (Sondheimer et al., 1961). Similarly other workers also described the 1:1 caffeine:chlorogenate complexation using nuclear magnetic resonance (NMR) (Horman et al., 1972). The study determined the association constant and identified the portion of chlorgenate ion involved in the complex formation. Further, they were also proposed that the plane of the caffeine molecule is parallel to the plane of the aromatic ring of the caffeoyl ester group and the five and six-member rings of nitrogen heterocycle are equally involved in the complex formation. Apart from the above mentioned studies recently there was report on the complexation of caffeine with 3-caffeoylquinic acid (3-CQA) and caffeine-chlorogenate complex in freshly prepared coffee brew by high resolution ^{1}H-NMR (D'Amelio et al., 2009).

Although, there are various studies reports existed on the complexation of caffeine with aromatic hydroxyl acids and caffeine-chlorogenate using NMR and spectrophotometer, however, there is lack of reports on the complexation of 5-CQA-CA. Further, the previous study of (D'Amelio et al., 2009) focuses on the complexation of CA-CAQ that is the titration of caffeine by 3-caffeoylquinic acid solutions. In coffee beans 5-CQA is responsible for 56-62 % of the total of chlorogenic acid according to the study of (Clifford and Wight, 1976), needs further studies on this areas. Therefore, in view of the extensive worldwide consumption of foods contain 5-CQA and caffeinated beverages and consequent possible effects existed, investigating the association constant and structural feature of the complex of 5-CQA-CA are a necessary.

Hetero-Association of Caffeine with Drugs and Dyes

Caffeine is also capable of interacting directly with several genotoxic aromatic ligands by stacking aggregation. The effects of CA on drugs efficiency in cellular systems has been carried out with drugs in the concentration range 0.01- 1 mM and CA in the concentration range 1-20 mM (Piosik et al., 2010; Baranovsk et al., 2009; Zdunek et al., 2000).

It forms the hetero-association complex with some dyes and aromatic drugs, such as acridine orange (Lyles and Cameron, 2002), erhidium bromide (Piosik et al., 2010; Baranovsk et al., 2009; Zdunek et al., 2000), methylene blue (Hayashi et al., 2004)], with anticancer drug: doxorubicin, mitoxantrone, daunomycin (Pioski et al., 2005; Piosik et al, 2002; Evstgneev et al., 2006), the antibacterial agent norfloxacin (Evstgneev et al., 2006), vitamin B_2 derivative flavinmononucleotide (Evstgneev et al., 2006) ,drug reduces risks of cardiovascular disease and chemoprevative agent for colorectal cancer, acetyl salicylic acid (Fouad et al., 2010) and with nucleic acids (Kan et al., 1980). The hetero-association of CA, with aromatic drugs and dyes diminish the pharmacological activity, which often related to its direct interaction with DNA (Lyles and Cameron, 2002; Piosik et al., 2010; Baranovsk et al., 2009; Zdunek et al., 2000; Pioski et al., 2005; Piosik et al, 2002; Evstgneev et al., 2006; Evstgneev et al., 2005; Kan et al., 1980). There are two approaches explaining these phenomena on one hand, caffeine is regards as an interceptor of aromatic molecules (Larsen et al., 1996; Traganos et al., 1991; Kapuscinski and Kimmel, 1993), and the other, as protector with respect cellular DNA. The interceptor mechanism involves the formation of the hetero-complexes, which leads to drop in the concentration of the ligand monomers, which bond to DNA and therefore, to lessening of their toxicity. The other is protector mechanism shows up as a competition among various kinds of ligands for bonding sites with DNA.

The hetero-association of CA with different aromatic molecules has been investigated using different mathematical model and analytical procedures to interpret the experimental results (Weller et al., 1984; Aradi and Folder 1985; 1989; Kapu Seinsky and Kimmel 1993; Chen and Shiao 1994; Baxter et al., 1996; Larsen et al., 1996; Bolotin et al., 2006; Baranovsk et al., 2009; Baranovsk et al., 2007). However, most of the proposed models of the molecular hetero-associations are only cover limited sets of condition used to analysis UV-Vis spectroscopy measurements of CA-drugs complexation (Larsen et al., 1996) only considered formation of 1:1 hetero-complexes without taking in to account the self-association of aromatic molecules in the solutions. Another model used to interpret optical spectroscopy data on the hetero-association of aromatic molecules took in to consideration limited to dimerization (Kapuscinsic and Kimmel 1993) and (Zdunek et al., 2000) the indefinite association model was used for self-association of one component, although the second component has negligible self-association under the condition of the experiment.

A model developed for NMR investigation of the equilibrium association of CA and methyl gallate (Baxter et al., 1996) is not satisfactorily as it uses rather approximation expression for monomeric concentration of one of the component in the mixed solution. Utilization of dimer model for molecular self-association in the analysis of the hetero-association of aromatic compounds (Aradi and Foldesi 1985, 1989) is confined to relatively small concentration of the interacting molecules, as is the graphical method for determination of hetero-association parameters (Chen and Shiao 1994).

A general statistical thermodynamic model of mixed-association of two substances forming indefinite aggregates for both self-association and hetero-association was used by Weller et al, (1984) for NMR studies of the hetero-association of CA and 5'=AMP, however the equation used in this model do not allow the concentration of each type of complex to be calculated, which is necessary for the analysis of competitive binding.

A statistical thermodynamic model of hetero-association, which also takes in to account for the formation of indefinite aggregates for both self-association and hetero-association of the molecules developed by (Davies, 1999) provide analytical expression for interpretation of NMR parameters of the interacting molecules in the mixed solutions. The model analytical enables both the structural and thermodynamic properties of hetero-association of complex to be determined from measurement of proton chemical shift of the molecules as a function of concentration and temperature (Davies, 1999).

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